REMARKS

1. Based on the Office Action and Office communication, the applicants have amended the claims to overcome the claim objection. The Claim 1 has been amended to add the limitation of "small-sized haematopoietic cells" [0029], which contain red blood cells, platelets and leukocytes. The claim 1 is also amended to specify the medium in step (b) to describe the culturing process.

2. Claim 32 should be canceled in that the step of removing cells not adhered on the plate by changing a culture medium has been added to Claim 1. Claims 39 and 40 should be canceled.

3. As the applicants mentioned, Caplan et al. used Leukosorb™ filter to remove fat, red blood cells and plasma. (column 46 line 14~15) However, the Leukosorb™ or its derivatives, which adsorb or trap leukocytes, can not remove leukocytes, as pointed by one patent (WO/2005/042784: DEVICE AND METHOD FOR HIGH-THROUGHPUT QUANTIFICATION OF MRNA FROM WHOLE BLOOD).

"Three anticoagulants were tested: ACD, EDTA, and heparin, with heparin resulting in the highest percent of leukocyte retention. While Leukosorb membranes have been used for ACD blood in transfusion, **approximately 15-40% of leukocytes passed through** even when four layers of membranes were simultaneously used. EDTA blood was tested; the capacity and leukocyte retention was found to be similar to those for ACD. Most notably, however, **was that 100% of the leukocytes in heparin blood were trapped on the Leukosorb membranes**. The capture of 100% of leukocytes from heparin blood shows the reliability of quantification of mRNA using the present invention. These data indicate that the use of heparin blood is most suitable for the precise quantification of mRNA, whereas ACD blood is useful for applications requiring larger volumes of blood and less quantitative results." (cited the WO/2005/042784)

As indicated by Caplan et al., heparin was used (column 45 line 55-57, column 46 line 49). The percentage of leukocyte captured by Leukosorb™ will be 100%. Therefore, a monoclonal antibody separation is then needed to separate mesenchymal stem cells. (column 46 line 35~61)

The Leukosorb™ or its derivatives trap leukocytes. However, on the opposite, the application used upper plate with pores to remove small-sized

haematopoietic cells including leukocyte. The Leukosorb™ traps leukocytes would teach away this application to remove leukocytes. Therefore, it would have not been obvious to one of ordinary skill in the art at the same time the upper plate taught by this application was made by modification from the Leukosorb™ used by Caplan et al.

Since the small-sized haematopoietic cells are added in Claim 1, it would not be obvious over Caplan et al's Leukosorb™ filter.

4. In the Supreme Court's KSR case, the patented technology combined an adjustable throttle pedal for an automobile with an electronic sensor to measure the pedal depression. Both of these features were in the prior arts. One of the prior arts claimed an adjustable pedal like the patent in litigation. Another patent disclosed electronic calibration features similar to patented technology in suit.

However, as the Office Action indicated, Rieser et al teach that bone substitute plate (7) serves two functions: it is a permeable wall for the cell space (1), and it provide a substrate for adherence of cells. Moreover the abstract of Rieser et al clearly indicated that "The cells settle on such a plate (7) and the cartilage tissue growing in the cell space (1) **grows into pores or surface roughness of the plate**, whereby an implant forms which consists of a bone substitute plate (7) and a cartilage layer covering the plate and whereby the two implant parts are connected to each other in positively engaged manner by being grown together."

Therefore, the applicants believe that this application is quite different from that of the Supreme Court's KSR case.

4. The plate taught by Rieser et al. is made of hydroxyapatite. Hydroxyapatite (calcium phosphate) is the inorganic matrix of bone tissues. Mesenchymal stem cells when cultured in expansion medium without any osteogenic differentiation additives will develop to osteoblast (Abstract, in Journal of Cellular and Molecular Medicine 12:281-291, 2008). Because bone cells such as osteoblasts will lay down osteoid (contains calcium phosphate) and transform into osteocytes embedded in mineralized bone matrix (Abstract, in Dev Dyn. 235:176-190, 2006), mesenchymal stem cells cultured on plate used by Rieser et al will differentiate into osteoblasts and buried themselves in mineralized bone matrix such as hydroxyapatite even in the medium used for expansion.

Consequently, the differentiated mesenchymal stem cells will not maintain as undifferentiated cells and will be difficult for isolation. Therefore, the difference between this application and the prior arts cited would not be obvious. As described in Claim 1, this application requires the medium containing factors that stimulate mesenchymal stem cells growth without differentiation and allowing for the selective adherence of only the mesenchymal stem cells to upper plate.

"Indeed, cells on calcium phosphate without osteogenic differentiation additives developed to osteoblasts as shown by increased ALP activity and expression of osteogenic genes, which was not the case on tissue culture plastic." (Cited in Calcium phosphate surfaces promote osteogenic differentiation of mesenchymal stem cells. Journal of Cellular and Molecular Medicine 12:281-291, 2008)

"During osteogenesis, osteoblasts lay down osteoid and transform into osteocytes embedded in mineralized bone matrix." (Cited in Buried alive: how osteoblasts become osteocytes. Dev Dyn. 235:176-190, 2006)

5. Regarding the obvious rejection over Caplan et al. in view of Prockop et al. and Mastui et al., the Office Action indicated that "Caplan et al. do not teach the method of isolating mesenchymal stem cells where the mixed population of cells in medium is seeded into a culture device..." It should be stressed here that US patent 5811094 (Caplan et al.) and 4871674 (Matsiu et al.) were issued on September 2, 1998 and October 3, 1989. However, up to the application date of US patent 7374937, October 25, 2000, Prockop et al. still described that "That is, prior to the disclosure provided herein, most stem cells were difficult to isolate and to expand in culture (i.e., it was difficult to induce them to proliferate in sufficient number)." (Column 11 lines 36-39) and "Another difficulty encountered using mesenchymal stem cells cultured using prior art culture/expansion methods is that mesenchymal stem cells produced using such methods retain reduced differentiative capacity." (column 11 lines 47-50)

This foreign priority date of this application is October 17, 2000, that was a week earlier than the application date of Prockop et al. As sated by Prockop et al., most stem cells were difficult to isolate and to expand in culture. Especially, none of the references cited isolates and cultures mesenchymal stem

cell in the same time. Therefore, it would not have been obvious to one of ordinary skill in the art to modify those references cited before October 17, 2000.

In sum, not only the steps of this application are different from the prior arts, but also there are no reasons to find this application in light of the teachings of the references. Accordingly, this application should be placed in condition of allowance. An early Notice to this effect is respectfully expected.

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